IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Tripp et al.
Application No. 09/889,317
Filed: July 13, 2001
Confirmation No. 2319
For: METHOD FOR THE PREVENTION AND TREATMENT OF DISEASES CAUSED BY AN INFLAMMATORY RESPONSE MEDIATED BY ENDOGENOUS SUBSTANCE P BY USING ANTI-SUBSTANCE P ANTIBODIES
Examiner: Francois P. Vandervegt
Art Unit: 1644
Attorney Reference No. 6395-59041-01

CERTIFICATE OF MAILING

I hereby certify that this paper and the documents referred to as being attached or enclosed herewith are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: MAIL STOP AMENDMENT, COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450 on the date shown below.

Attorney or Agent for Applicant(s)_____

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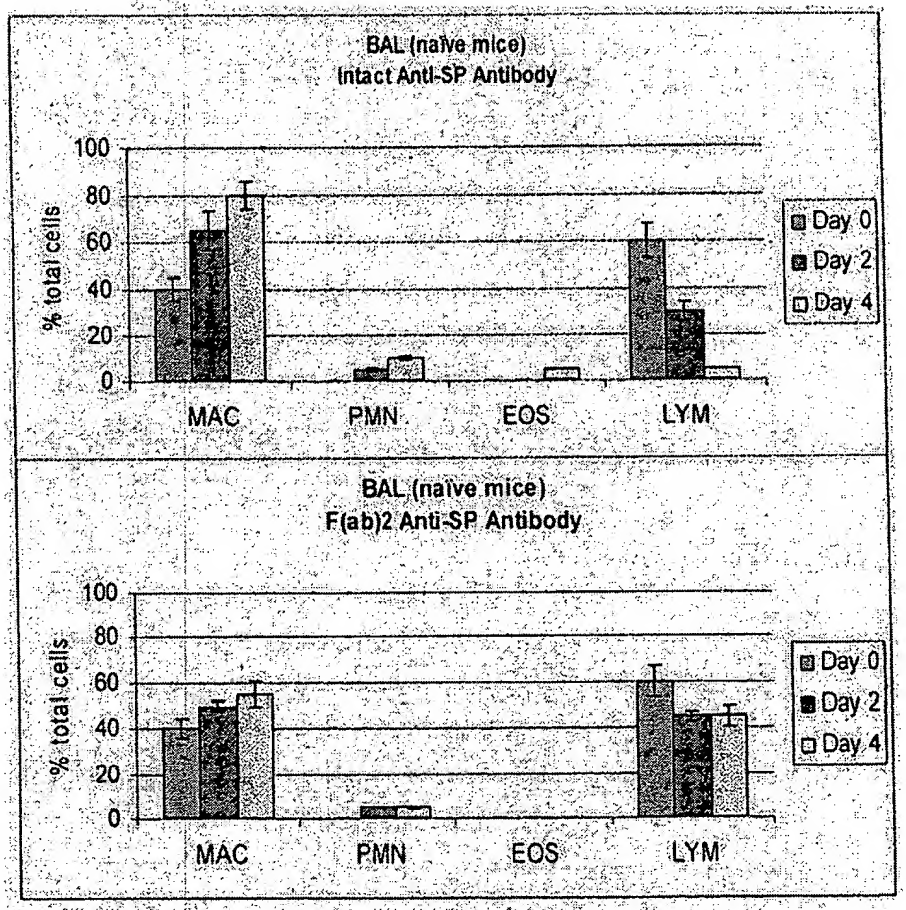
DECLARATION OF RALPH A. TRIPP UNDER 37 C.F.R. § 1.132

1. I, Ralph A. Tripp, am an inventor of the above-referenced patent application. I was employed by the Centers for Disease Control and Prevention, the assignee of the above-identified pending patent application. I hold a Ph.D. degree in immunology, and have expertise in RNAi therapeutics, innate and adaptive immune responses to respiratory viral infections, cytokines, chemokines and host cell defense mechanisms. I was employed by the Centers for Disease Control and Prevention for 7 years studying the mechanisms of immunity and disease pathogenesis associated with respiratory virus infections. I currently hold the position of Professor & GRA Chair, Department of Infectious Disease, at the University of Georgia, College of Veterinary Medicine in Athens, GA.

2. I have read the specification of the above-referenced application, and the Office action, dated April 8, 2005. It is my understanding that claims 1-3, 5, 13, 14, 19-21, 23, 31, 32, 41, and 42 have been rejected as allegedly being obvious.

3. A major limitation in the effectiveness of monoclonal antibodies is immunogenicity of the monoclonal antibody itself; the development of an inflammatory response following administration can significantly limit the usefulness of an antibody. The immunogenicity of antibodies that specifically bind an antigen of interest (such as substance P), or fragments of this antibody, cannot be predicted. In addition, the route of administration can affect the immunogenicity of an antibody; the effect of the route of administration on immunogenicity also must be determined experimentally. It was tested if intranasal administration of intact antibodies would result in greater pulmonary inflammation compared to $F(ab')_2$ anti-substance P antibody fragments in naïve mice. Intraperitoneal delivery was directly compared with intranasal delivery; intranasally administered $F(ab')_2$ anti-substance P antibody fragments provided an unexpectedly superior reduction of inflammation in naïve mice as compared to intraperitoneally administered $F(ab')_2$ anti-substance P antibody fragments.

Naïve mice were treated with 0.05 ml of 200 μg/ml intact anti-substance P antibodies or anti-substance P $F(ab')_2$ antibody fragments diluted in PBS. Bronchoalveolar lavaged leukocytes were collected from 4-6 naïve mice/experiment on days 0, 2 and 4 post-treatment, and the experiment repeated three times. Collected bronchoalveolar lavaged leukocytes were spun onto microscope slides, fixed, and hematoxylin and eosin stained to determine the percentage of macrophages (MAC), polymorphonuclear leukocytes (PMN), eosinophils (EOS) or lymphocytes (LYM) based on the $\geq$200 cells counted/slide. When naïve mice were treated intranasally intact anti-substance P antibodies or anti-substance P $F(ab')_2$ antibody fragments diluted in PBS, the results were obtained:



The results show that naïve mice intranasally administered $F(ab')_2$ anti-substance P antibody fragments had reduced pulmonary inflammation (as indicated by reduced infiltration of macrophages, polymorphonuclear leukocytes, and eosinophils) as compared to mice intranasally administered intact anti-substance P antibodies. Thus, intranasal administration of $F(ab')_2$ anti-substance P antibody provide an unexpected superior reduction in pulmonary inflammation.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Ralph A. Topp

8/5/05
Date